REMARKS

Interview

Applicant thanks the Examiner for agreeing to discuss the posture of this case at this stage of prosecution. During the interview, the recently cited art was discussed and a proposal for claim amendments was reviewed. Emphasis was made to point out to support and enablement of claims when amended. Applicant sincerely believes that the concerns so outlined during the interview are fully addressed by the amendment and remarks presented in this Reply.

Support for claims amendment:

Claim 1 is amended to recite a macromer having a "group crosslinkable by a free radical chain reaction" and where the crosslinking of the macromer is "performed by a free radical chain reaction." Support for this amendment may be found in the specification at least on page 8, lines7-13 (or as published at paragraph [0016]) page 14, line 13 (or paragraph [0033]) and in original claim 7).

Claim 6 is amended to change the claim dependency and recite the crosslinking step to occur (while in the frozen state) via UV, visible or IR radiation. Support for this amendment can be found in the specification at least on page 8, lines 3 (or paragraph [0016]), and in Examples 9-10 pages 30-31 (or paragraphs [0073-0075]).

Claim Rejection under 35 USC §103(a)

1. Claims 1-13, 15 and 16 are rejected under 35 USC §103(a) as allegedly being obvious over by DeLuca et al. (US Patent 4,741,872), Yannas et al. (US Patent 4,955,893), Allen et al. (US patent 4,962,172), and Solomon et al. (US patent 5,484,604). Applicant has amended the claims to recite that the macromer has groups crosslinkable by free radical chain reaction, and that the step of crosslinking is performed via free radical chain reaction. Applicant believes that the present claims are patentable over the cited combination as the combination does not teach as a whole the claimed process and neither reference provides any motivation to combine the various features of their teaching to arrive at the presently claimed invention.

The present invention is directed to materials prepared by crosslinking macromers in the dry or frozen state by free radical chain reactions occurring between the free radical reacting

groups of the macromers. When the macromers are present in aqueous solution, the various hydrophilic and lipophilic groups of which they are made arrange themselves to form microstructures such that the free-radical reacting groups are gathered in close proximity of one another in the form of micelles.[1] The present inventors have found that these microstructures are preserved while converting the solution to the frozen or dry state and that activation of the free-radical groups congregated within these micellar micro domains is easily and efficiently triggered in the dry or frozen state by application of heat or light radiation, which both have the ability to penetrate the material in the dry or frozen state. Once activated, these groups react with one another as they are confined in close proximity thus crosslinking the macromer. The chain reaction need not be long lived to create effective crosslinking.

Neither DeLucas or Yannas teaches processes in which the crosslinking occurs in the solid state such as the frozen or dried state as presently claimed here. DeLucas only teaches a process in which the crosslinking occurs in the liquid state. Yannas only teaches a process for freeze-drying. The polymer is provided either in the uncrosslinked or as already crosslinked.

Allen does not cure the deficiencies of DeLucas or Yannas, as Allen does not teach crosslinking in the dry or frozen state, nor crosslinking by free radical polymerization reaction. Allen merely teaches reaction of crosslinking by esterification mostly conducted under heat or with the presence of a catalyst with the polymer present in solution. The examiner points to claim 20, to support the combination. However, claim 20 recites "the fiber or film is dried after the precipitation and before the formation of the cross linkages". Also, at col. 7, lines 24-25, while Allen mentioned that the "linear polymer may initially be dry" it goes on to teach that "it may then be wetted and crosslinked so as to cause adhesion and cross linking" indicating that the crosslinking step is occurring in a wet or liquid phase and not in the dry phase. Thus this teaching is insufficient in that it does not clearly teach that the crosslinking occurs in the dry or frozen state.

Solomon also does not cure the deficiencies of DeLucas or Yannas, as Solomon also does not teach crosslinking in the dry or frozen state or crosslinking by free-radical polymerization. Solomon only teaches devices made of an ionically crosslinked matrix. While the precursor

[1] See abstract Barman S.P., *et al.*, "Biodegradable In-Situ polymerizable Macromers as matrices for targeted Drug Delivery", *Proceed. Inter. Symp. Control Rel. Bioact. Mater.*, 22 (1995) (copy attached in appendix herewith)

polymer may be initially dried before the crosslinking, the crosslinking step is taught as occurring upon exposure to ionic solutions by spraying onto the dry material (see example and claim 1). It is questionable that Solomon can be seen as teaching crosslinking in the dry state, as the ions would have no means of migrating within the matrix absent a solvent vehicle. Solomon probably teaches merely interfacial crosslinking at the interface of the dry material and the sprayed solution, which when applied onto the polymer partially solubilizes then crosslinks the polymer strands.

Because Solomon and Allen, in which the crosslinking nucleophilic or ionic reaction, show that a medium such as a solvent is required to transport the reagents to their reactive sites to induce crosslinking reactions, they provide no motivation to the skilled artisan to combine their teachings with those of Delucas and or Yannas to arrive at the presently claimed process.

Even when combined, these references still failed to teach crosslinking in the dry or frozen state as outline above. Applicant thus submits that the claimed process is patentable over the cited art and respectfully request that the rejection be withdrawn.

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Biodegradable In-Situ Polymerizable Macromonomers as Matrices For Targeted Drug Delivery

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Introduction:

The objective of targeted drug delivery is to release a biologically active agent in a predictable and controlled manner at the site where it is needed most. Advances in modern surgery provide access to the deepest internal organs with minimally invasive devices. Using techniques such as laparoscopy, macromonomers can be deposited and subsequently polymerized inside the body. This method of "on-site" polymerization achieves unique advantages such as conformity to specific organs and adherence to underlying tissue(1). Amphiphilic block copolymers in aqueous formulations tend to aggregate to form micro micellar domains. The hydrophobic segments of the molecules order themselves in the interior of these domains ("the core"), the exterior being comprised of hydrophilic segments ("the corona"). These microscopic "cores" can act essentially as containers for hydrophobic drugs, thus providing microreservoirs for sustained drug release(2). The fundamental parameter of this supramolecular assemblage of amphiphilic polymers in aqueous solution is the Critical Micellar Concentration (CMC), which can be defined as the lowest concentration at which the dissolved macromolecules begin to self-assemble.

This paper reports synthesis and characterization of micelle-forming biodegradable monomers. Copolymers of PEG (molecular weight 8000) with different combinations of polycaprolactone and polyglycolate were synthesized and then endcapped with acrylate moieties. The ability of these monomers to solubilize model hydrophobic drugs is demonstrated by a systematic study of the CMC through the gradual dissolution of a molecular probe, 1,6 Diphenyl 1,3,5-Hexatriene (DPH).

Materials and Methods:

Synthesis:

The molecular structures of the monomers are given in Figure 1. Polyethylene glycol 8000 (Union Carbide) was melt-dried at 100-110 ^{0}C in vacuum (10-15 mm Hg) for 4-6 hours. Caprolactone (predistilled, Aldrich) was charged into a Schlenk-type reaction vessel and stannous 2-ethyl hexanoate (Sigma) was added as a ring opening catalyst. The reaction was carried out for 4 hours in an inert atmosphere at 180 ^{0}C. The reaction mixture was then cooled to 80 ^{0}C, dissolved in toluene, precipitated in hexane and the product was collected by vacuum filtration. The product was redissolved in toluene and dried by azeotropic distillation. Acrylation was carried out by the dropwise addition of a 2 molar excess of acryloyl chloride and triethylamine under a nitrogen flush at 65 ^{0}C for 1 hour. By-product salts were removed by vacuum filtration. The product was isolated by precipitation in a large excess of hexane followed by vacuum filtration. The monomers were characterized by NMR on a Varian 300 MHz Nuclear Magnetic Spectrometer.

Determination of Critical Micellar Concentrations:

A hydrophobic dye 1,6, Diphenyl 1,3,5-hexatriene (Aldrich), (DPH), which demonstrates enhanced absorbance (358 nm) at the CMC due to associative interactions was used in this study (3). A stock solution of DPH was prepared in methanol (0.4 mM). Aqueous monomer solutions were prepared by dissolution in PBS and dilution to the desired concentrations. 10 µl of the dye solution were added to each vial with equilibration for at least 1 hour. The absorption spectra of the polymer/dye/water solutions were recorded in the 250-500 nm range using a Hitachi UV-VIS Spectrometer.

Photopolymerization:

Photopolymerization of the polymer solutions were carried out in both visible and ultraviolet light systems as described in (4).

In Vitro degradation:

200 µl of 10% monomer solution were UV polymerized to form a gel. The degradation of the hydrogels was monitored at 37 ^{0}C in PBS.

Results and Discussion:

Hydrophobic segments of these monomers were changed by using various combinations of caproate and glycolate linkages in the molecule. The critical micellization point was obtained from the first inflection of the absorption vs. concentration curve. These curves are shown in Figure 2. It is clearly evident from the curve that the solubility of the dye is enhanced with increasing concentration of the monomer. The CMC values for various monomers are listed in Table 1. The CMC value is lowered with increase in caproate content of the monomer. This is expected due to the tighter aggregation of the hydrophobic caproate moieties. The fast gelling ability of these monomers under UV and visible light are shown in Table 1. The gel times

range between 4-12 seconds. The photopolymerized hydrogels degrade under aqueous conditions. The degradation times i.e., times to complete dissolution, varied from 10 - 44 days , increasing with cap/gly ratio. The fast gelation times of these monomers, their ability to dissolve hydrophobic solutes and their controlled degradation rates render them excellent candidates for localized drug delivery.

References:

1) Hill-West J. L., Chowdhury S. M., Sawhney A. S., Pathak C. P., Dunn R. C. and Hubbell J. A., *Obstetrics & Gynecology*, 83, 59 (1994)

2) Kataoka K., Kwon G. S., Yokoyama M., Okano T. and Sakurai Y., *J. Controlled Release*, 24, 119 (1993)

3) Alexandridis P., Holzwarth J. F. and Hatton T. A., *Macromolecules*, 27, 2414 (1994)

4) Sawhney A. S., Pathak C. P. and Hubbell J. A., *Macromolecules*, 26, 581 (1993)

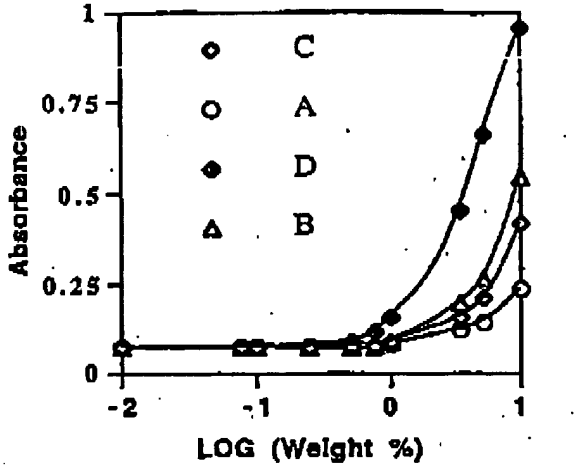
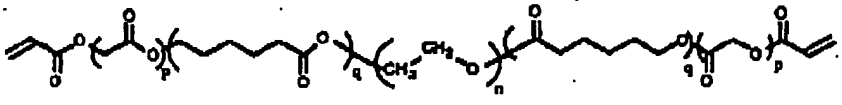


Figure 2: Effect of monomer concentration on absorption intensity of DPH at 356 nm.

Table 1: Aggregation and Photopolymerization Properties of Monomers.

Monomer	Critical Micellar Concentration (%)	Gel* Time Initiated Using UV Light (secs)	Gel** Time Initiated Using Visible Light (secs)	Total Degradation time (days)
A	0.92	5.5±0.4	8.9±0.1	10
B	0.55	5.8±0.1	8.2±0.5	14
C	0.32	5.2±0.2	9.8±0.4	18
D	0.28	4.6±0.1	10.4±0.3	44

* 2,2-Dimethoxy2-phenylacetophenone as UV initiator, Long UV light, 20% monomer conc.
** Eosin, triethanolamine initiating system; green light source, 20% monomer conc.



PEG - Caprcate - Glycolate - Acrylate, n = 182
Monomer A : p = 4, q = 1; Monomer B: p = 3, q = 2; Monomer C : p = 2, q = 3; Monomer D : p = 1, q = 4
p and q are randomly distributed

Figure 1: Structure of macromonomers